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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/103,745	06/24/1998	SUDHIR AGRAWAL	475.08.642CI	3401

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EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/103,745	AGRAWAL, SUDHIR	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 2/15/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 11/13/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 2/15/07, claims 1 and 3–5 are pending in the application and under examination.

Terminal Disclaimer

The terminal disclaimer filed on 2/15/07 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent 5,856,462 has been reviewed and is accepted. The terminal disclaimer has been recorded. Accordingly, the rejection of Claims 1 and 3-5 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,856,462 is withdrawn.

Claim Objections

Claims 4 and 5 are objected to because of the following informalities:

Claim 4 recites "A method for providing c ..." The term "c" in this preamble may be a typo.

At Claim 5, penultimate line, is the clause "fewer side effects that ...." The word "that" may be a typo. Applicant may have intended "than."

Clarification and/or correction is required.

Claim Rejections - 35 USC § 112, second paragraph—withdrawn

The rejections of Claims 1 and 3–5 under 35 U.S.C. 112, second paragraph, as being indefinite are withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 112, first paragraph—withdrawn

The rejection of Claims 1 and 3–5 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter rejection) is withdrawn in view of Applicant's amendments to the claims.

Claim Rejections - 35 USC § 102—reinstituted, necessitated by amendment

Claims 1 and 3-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Cook (U. S. Patent Number 5,212,295) for reasons of record. See the Non-Final Rejection mailed 8/24/05 and the Final Rejection mailed 1/25/06.

The instant rejection is reinstituted in view of Applicant's amendment to the claims, filed 2/15/07, removing the term "racemic."

Response to Arguments

In the remarks filed 2/15/07, Applicant argues Cook fails to teach a CpG-containing phosphorothioate oligonucleotlde or any other type of oligonucleotide. Applicant contends Cook only describes monomers that can be used in the preparation of oligonucleotides. Applicant states Cook does not teach the immune stimulating properties of the CpG dinucleotide or that the claimed modifications to the CpG dinucleotide can reduce the side effects (i.e., immune-stimulation) of antisense oligonucleotides having this dinucleotide. Accordingly, Applicant argues, Cook fails to anticipate Claims 1 and 3-5.

Applicant's arguments filed 2/15/07 have been fully considered but they are not persuasive.

The basis for the rejection over Cook has been described in at least two previous Office Actions (cited above). The reasoning applied therein remains applicable to the claims as now presented.

Applicant's characterization of Cook is inaccurate. Cook describes methods and materials for making and using chirally pure, backbone modified antisense oligonucleotides for diagnostic and therapeutic purposes. Preferred embodiments include phosphorothioated antisense oligonucleotides comprising one or more 2'-O modified nucleotides (see col. 9, for example).

It is stated that chirally pure oligos synthesized according to the disclosed methods are expected to exhibit one or more efficacious properties such as, for example, hybridization with targeted RNA's and DNA's, cellular absorption and transport, or improved enzymatic interaction, and that further improvements may be made by substitutions or modifications to the base or the sugar moieties of the individual nucleosides employed to prepare the chiral oligonucleotides of

the invention (col. 10). A limited number of specific 2'-O substituents are explicitly identified as preferred for such use.

Specific oligonucleotides are explicitly set forth at column 13 by the disclosure of recommended target regions in specific genes. In some cases, the oligonucleotides complementary to these 18-nucleotide target regions comprise CpG dinucleotides. See antisense oligos recommended for HPV-11, -18 and for ras. Thus, Cook does in fact teach specific CpG-containing oligonucleotides, that such oligos should be contain chirally pure phosphorothioate linkages, and that the oligo be further improved through modification to one or more sugar and/or base moieties, including the use of 2'-O modifications such as those listed in column 10, as explained in the Office Actions of 1/25/06 and 8/24/05. Furthermore, the oligos are specifically taught for administration to organisms and animals, for in vivo applications (cols. 12 and 13).

It is not necessary for Cook to have taught or recognized any or all other properties inherent to such oligonucleotides to anticipate the claimed inventions. Cook discloses the claimed oligonucleotides and that is sufficient for anticipation under 35 USC §102. ""[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." See MPEP §2112.

Accordingly, Cook anticipates the instant claims.

Claim Rejections - 35 USC § 102—new, necessitated by amendment

Claims 1 and 3–5 are rejected under 35 U.S.C. 102(b) as being anticipated by Agrawal et al. (WO 94/01550).

Agrawal et al. disclose self-stabilized, hairpin oligonucleotides comprising target hybridizing and self complementary regions that form a totally or partially double stranded structure that is resistant to nucleolytic degradation (pg. 5, lines 13-17, 25–30). The self-stabilized oligonucleotides are specifically designed for inhibiting gene expression in vitro and in vivo by inducing RNase H-mediated cleavage of a target mRNA (pages 5-6).

It is taught that the target hybridizing and a self complementary regions of the oligonucleotide can be composed of ribonucleotides, deoxyribonucleotides, or both, with ribonucleotide and/or deoxyribonucleotide monomers being connected together via 5' to 3' linkage (pages 8–16, for example). It is taught that the oligonucleotide may include modified nucleic acid bases and/or sugars as well as molecules having added substituents, such as diamines, cholesteryl, or other lipophilic groups.

At page 16 it is taught that the self-complementary region may contain ribonucleotides, deoxyribonucleotides, analogs of ribonucleotides or deoxyribonucleotides having artificial linkages, or combinations of any of the above. It is further taught that the ability to activate RNase H is not important for the self-complementary region, so nucleotides having artificial linkages that do not activate RNase H can be used in this region without diminishing the effectiveness of the oligonucleotide. Thus, in addition to phosphodiester and phosphorothioate or phosphorodithioate linkages, this region may also or alternatively contain phosphoramidate

(including N-substituted phosphoramidates), alkylphosphonate, alkylphosphonothioate linkages as well as non-phosphate containing linkages, such as sulfone, sulfate, and keto linkages.

It is further taught that in one preferred embodiment, the self-stabilized oligonucleotide is rendered hyperstabilized by incorporating in to the self-complementary region one or more 2'-O-methyl ribonucleotides. Agrawal et al. show a specific embodiment of such an oligonucleotide at Fig. 5, compound C. Compound C contains one (1) CpG dinucleotide in the self-complementary region. Synthesizing the embodiments of this compound specifically taught by Agrawal et al. would necessarily result in the production of a CpG-containing antisense oligonucleotide having a 2'-O-methyl-modified CpG. Additional representative embodiments, including as series of hairpin, CpG-containing oligonucleotides said to have anti-HIV activity and which are directed to a portion of the gag region of the HIV-1 genome are shown in Fig. 5 and Examples 1-3, pp. 20-28.

If that is not enough, Agrawal et al. teach that in phosphorothioated, self-stabilized antisense oligos as taught at page 16, the target hybridizing region may contain 2'-O-Me ribonucleotides (i.e., uniformly modified) (page 16, bottom). Compound C synthesized according to this embodiment would comprise at least one 2'-O modified CpG.

Agrawal et al. teach and claim that their self-stabilized, backbone modified antisense oligonucleotides may be used for therapeutic purposes to inhibit gene expression in a human or other mammal, such as, for example, to treat a disease arising from a virus or pathogenic organism infection (see claim 19, for example, and page 18). Methods of administration are described (page 18-19).

Accordingly, Agrawal et al. anticipates the instant claims.

Response to Arguments

In response to the previous rejection over Agrawal et al. as evidenced by Cook, Applicant argues Agrawal does not specifically teach the modifications of the CpG dinucleotide or that such modifications reduce the side effects of oligonucleotide therapy.

Applicant's argumentshave been fully considered but they are not persuasive.

While Agrawal et al. do not specifically teach that backbone modifications should be specifically incorporated into CpG spots, Agrawal et al. teach incorporating phosphorothioate and other backbone and sugar modifications throughout either the self-complementary or target-hybridizing regions of virtually any self-stabilized antisense oligonucleotide, including the specific, CpG-containing, anti-HIV sequences represented in the Figures and described in the specification. See in particular Compound C, Fig. 5, recommended for use against HIV-1 (page 20 and 22-27).

Agrawal et al. point to the self-stabilized region as particulary amenable to modification since it is not needed for Rnase H activity. The self-stabilized region of Compound C, for example, is only 12 nucleotides long and contains only one 5'CpG3'. Hyperstabilized embodiments of this oligo according to Agrawal et al. include oligos within the scope of the instant claims. Moreover, as explained above, Agrawal et al. taught a phosphorothioated embodiment of Compound C comprising 2'-O-methyl ribonucleotides in the target hybridizing region, which compound and region contains at least one CpG dinucleotide.

Accordingly, Agrawal et al. teach each of the limitations of the instant claims.

While Agrawal et al. do not teach that such modifications reduce the side effects of oligo therapy, or render the oligonucleotides less immunostimulatory, this is an inherent property of

the oligonucleotides taught by Agrawal et al., and it is not necessary for Agrawal et al. to have taught or recognized this or any other inherent feature to anticipate the instant claims, so long as that feature is inherently present in the compounds taught. As the compounds disclosed by Agrawal et al. are identical to those now embraced by the instant claims, these properties must be present according to the instant claims.

As Applicant knows, ""[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." See MPEP §2112.

Claim Rejections - 35 USC § 102—new, necessitated by amendment

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Kawasaki et al. (1993) *J. Med. Chem.* 36:831–841.

Kawasaki et al. disclose a 15-nucleotide antisense oligonucleotide comprising a phosphorothioate backbone and a 2'-O-methyl modified CpG that is specific for human papilloma virus genome (see oligo #12 in Table 1, page 833).

Compositions thereof are also disclosed and tested (see pages 833–840).

Although, Kawasaki et al. do not teach that the disclosed oligo inhibits gene expression with "reduced side effects," the oligo disclosed meets the structural limitations of the claim and would necessarily possess this property.

"There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference." (MPEP 2112).

Accordingly, Kawasaki et al. anticipate the instant claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 3–5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawasaki et al., as applied to claim 1 above, in view of Agrawal et al. (WO 94/01550) and Shillitoe et al. (1994) *Cancer Gene Therapy* 1:193–204.

Kawasaki et al. is relied on for the reasons given above.

Kawasaki et al. did not teach steps for administering Oligo #12 of Table 1 to a mammal.

However, Kawasaki et al. explicitly recognized the antisense, Rnase H activity of each of the chimeric oligos disclosed therein, including the 2'-O-methyl modified, papilloma virus-

specific oligo 12 set forth in Table 1, and, on the basis of their studies, suggest applying the oligos against biological targets (page 837, right column).

Agrawal et al. set forth methods and materials for making and using self-stabilized, phosphorothiote antisense oligonucleotides against virtually any known viral or cellular gene, and specifically taught and suggested methods for administering such oligos to animals and humans for therapeutic purposes to treat a diseased human or animal in which the disease results from infection with a virus or pathogenic organism, or from the abnormal expression or produce of a cellular gene. The method comprises administering self-stabilized oligonucleotides according to the invention in a pharmaceutically acceptable carrier to the diseased human or animal (page 18 and claims 18-20).

Shillitoe et al. teach that papilloma viruses are etiological agents of cancer, and are often present in many cervical and oral cnacers.

It would have been obvious to one of skill in the art at the time the instant methods were invented to have made and administered the Kawasaki et al. oligos according to the methods taught by Agrawal et al.

One would have been well motivated and have had a reasonable expectation of success given that Kawasaki et al. taught that the oligos disclosed therein possess antisense activity against human papilloma virus, given that Agrawal et al. taught that chemically modified, self-stabilized antisense oligos are more resistant to nuclease degradation and more potent than conventional single-stranded antisense oligonucleotides, that such oligos are effective for treating viral infections, and that such oligos may be administered to humans for the treatment of

viral infections, and given that Shillitoe et al. taught that papilloma viruses may be the underlying cause of some forms of human cancer.

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Louis Wollenberger
Examiner, Art Unit 1635
April 6, 2007